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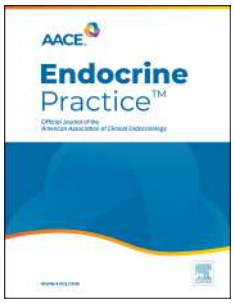

Vitamin D and Its Potential Benefit for the COVID-19 Pandemic

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Vitamin D and Its Potential Benefit for the COVID-19 Pandemic

Abstract

Vitamin D is known not only for its importance for bone health, but also for its biologic activities on other many other organ systems. This is due to the presence of the vitamin D receptor (VDR) in various types of cells and tissues, including the skin, skeletal muscle, adipose tissue, endocrine pancreas, immune cells and blood vessels. Experimental studies have shown that vitamin D exerts several actions that are thought to be protective against COVID-19 infectivity and severity. These include the immunomodulatory effects on the innate and adaptive immune systems, the regulatory effects on renin-angiotensin-aldosterone-system in the kidneys and the lungs, and the protective effects against endothelial dysfunction and thrombosis. Prior to the COVID-19 pandemic, studies have shown that vitamin D supplementation is beneficial in protecting against risk of acquiring acute respiratory viral infection and may improve outcomes in sepsis and critically ill patients. There are a growing number of data connecting COVID-19 infectivity and severity with vitamin D status, suggesting a potential benefit of vitamin D supplementation for primary prevention or as an adjunctive treatment of COVID-19. Although the results from most ongoing randomized clinical trials aiming to prove the benefit of vitamin D supplementation for these purposes are still pending, there is no downside to increasing vitamin D intake and having sensible sunlight exposure to maintain serum 25-hydroxyvitamin D at least 30 ng/mL (75 nmol/L) and preferably at 40 – 60 ng/mL (100 – 150 nmol/L) to minimize the risk of COVID-19 infection and its severity.

Keywords: Vitamin D, 25-hydroxyvitamin D, COVID-19, SARS-CoV-2

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the new strain of coronavirus that causes coronavirus disease (COVID-19) (1, 2). Due to the high infectivity and transmissibility of this novel virus, COVID-19 quickly became a global pandemic that has already affected at least 219 countries since its emergence from Wuhan, China in December 2019 (2, 3). The most common clinical manifestations of COVID-19 include fever, fatigue, anorexia, myalgia, cough, sputum production and dyspnea (4, 5). Although the majority of the COVID-19 patients are either asymptomatic or develop only mild respiratory symptoms, a significant number of patients develop severe complications that result in morbidity and mortality, including acute respiratory distress syndrome (ARDS), arterial and venous thrombosis, multi-organ failure, septic shock, among others (4, 5). Factors known to be associated with increased susceptibility to severe outcomes are advanced age, cancer, immunocompromised state, chronic kidney disease, chronic respiratory disease, cardio-metabolic disorders and smoking (6). The elderly, African Americans, patients with obesity and nursing home residents (7, 8) have disproportionately higher rates of infection, morbidity and mortality from COVID-19. These populations are also known as being at high risk for vitamin D deficiency (9-12). Thus, vitamin D deficiency could potentially contribute to higher COVID-19 positivity, morbidity and mortality rates appreciated in these populations.

Vitamin D is not only known for its importance for bone health, but also recognized for its potential protective effects against multiple chronic diseases as well as its immunomodulatory activities (10, 11, 13). With the global prevalence of vitamin D deficiency (defined by serum 25-hydroxyvitamin D [25(OH)D] level of <20 ng/mL) and insufficiency (defined by serum 25(OH)D level of 20 - <30 ng/mL), of 40 – 100% (14-17), correcting vitamin D deficiency would be a cost-effective intervention to alleviate the burden of this pandemic in a populational level. The aim of this review is to discuss potential biological mechanisms by which vitamin D could be protective against COVID-19 and to summarize evidence from observational studies and clinical trials that demonstrated the direct and indirect link between vitamin D and COVID-19.

Sources, synthesis and metabolism of vitamin D

Vitamin D is responsible for regulating calcium and phosphate metabolism and maintaining healthy mineralized skeleton. It is also known for its biologic activities on various types of tissues including the immune system (10, 11, 13, 18-20). There are two

forms of vitamin D: vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Vitamin D_2, synthesized from ergosterol, is found in sun dried and ultraviolet irradiated mushrooms and yeast, while vitamin D_3 is synthesized from endogenous 7-dehydrocholesterol in the skin and can be found naturally in oily fish and cod liver oil, as well as in meat in the form of $25(OH)D_3$ (10, 11, 21-23). Once entering the circulation, vitamin D (vitamin D_2 and D_3) is converted by several vitamin D-25-hydroxylases (*i.e.*, CYP2R1, CYP27A1, CYP2C11, CYP2J3, CYP3A4) in the liver into 25(OH)D, the major circulating metabolite of vitamin D. 25(OH)D is then metabolized by the 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) to the biologically active form, 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] (24). The kidneys are the main site of conversion of 25(OH)D into the circulating bioavailable $1,25(OH)_2D$, which is responsible for regulating intestinal calcium absorption and bone calcium mobilization (10, 11). Furthermore, CYP27B1 is expressed in several other tissues, including parathyroid glands, breast, colon, keratinocytes, microglia and immune cells where $1,25(OH)_2D$ is produced and exerts its autocrine, paracrine and intracrine functions by binding with the intracellular vitamin D receptor (VDR), which subsequently leads to up- or down-regulation of a multitude of genes (10, 11).

Vitamin D and immune function

Due to the presence of the VDR in most tissues, including the skin, skeletal muscle, adipose tissue, endocrine pancreas, immune cells and blood vessels, vitamin D has been shown to have a multitude of non-skeletal biological activities. In particular, vitamin D is considered an immunomodulatory agent that regulates both innate and adaptive immune systems (**Figure 1**) (10, 11, 13, 18-20). Activated macrophages express CYP27B1 that converts 25(OH)D into $1,25(OH)_2D$. $1,25(OH)_2D$, in turn, induces the macrophage production of the endogenous antimicrobial peptides, cathelicidins and defensins (18, 19, 25). Furthermore, $1,25(OH)_2D$ has been shown to alter the activity of different types of T helper cells by promoting a shift from T helper 1 (T_H1) and T helper 17 (T_H17) to T helper 2 (T_H2) immune profile and facilitating differentiation of regulatory T cells (T_{reg}) (26-29). In addition, both cytotoxic T lymphocytes (CTL) and B cells, when activated, upregulate their VDR, suggesting a coordinated regulation of the VDR signaling pathway and response to stimuli of these components of the adaptive immune system (30-32).

The effect of vitamin D supplementation on immune function has been well-demonstrated in a recent study that evaluated broad gene expression in peripheral blood

mononuclear cells (PBMCs) after orally supplementing various doses of vitamin D (33-35). Thirty healthy adults with vitamin D insufficiency [25(OH)D 20 - <30 ng/mL or 50 -<75 nmol/L] or deficiency [25(OH)D <20 ng/mL or <50 nmol/L] were randomized to receive 600, 4,000 or 10,000 IU per day of vitamin D_3 for 6 months and were found to have dose-dependent alteration in broad gene expression with 162, 320 and 1,289 genes up- or down-regulated in their PBMCs, respectively (33). Equally interesting if not more is that some individuals might respond to vitamin D more or less than others as high inter-individual difference in responsiveness to vitamin D supplementation has been observed (**Figure 2**)**.** In the same clinical trial, those who received this same dose of vitamin D and raised their serum concentrations of 25(OH)D to the same degree showed marked differences in the level of expression of the same genes (33). In addition, different patterns of serum metabolomic profile were also observed between the subjects with robust and minimum to modest genomic responses (33, 34). These observations support of the findings from a previous clinical trial that gave 3,200 IUs of vitamin D_3 per day to 71 prediabetic patients for 5 months and revealed robust changes in broad gene expression in PBMCs only in about half of the subjects despite comparable serum concentrations of 25(OH)D (35).

Potential protective effects of vitamin D against COVID-19

There are multiple biological explanations by which vitamin D could potentially be protective against infectivity and severity from COVID-19. These include vitamin D's immune- and non-immune- mediated actions on several tissues via both genomic and non-genomic pathways. First, $1,25(OH)_2D$ enhances the innate immune system by inducing not only the macrophages but also the respiratory epithelial cells to produce the antimicrobial peptide, cathelicidin LL-37 (36). This antimicrobial peptide not only acts against invading bacteria and fungi by destabilizing their cell membranes, but also exhibits direct antiviral activities against respiratory viruses by altering viability of host target cells and disrupting their envelopes (37-39). This mechanism is supported by the result of a pilot clinical trial that gave a single enteral dose of 400,000 IUs of vitamin D_3 or placebo to patients with sepsis and demonstrated an increase in serum cathelicidin in the treatment group compared with the placebo group (40). More interestingly, it has been recently demonstrated in an experimental study using surface plasmon resonance analysis that LL-37 competitively binds to SARS-CoV-2 S protein, which, in turn, inhibits viral binding to the receptor ACE2 and most likely prevents viral entry into the cell (41). In addition, cathelicidins were shown to prevent against lung damage associated with oxygen toxicity (42).

The second mechanism is related to the immunomodulatory effects of vitamin D on the adaptive immune system. As discussed in the previous section, $1,25(OH)_2D$ has been shown to down-regulate the activities of T_H1 and T_H17 and promote differentiation of T_{reg} (26-29). This leads to a decrease in the production of proinflammatory cytokines, including IL-6, IL-8, IL-12, TNL-α and IL-17 (26-29), thereby alleviating the cytokine storm syndrome in COVID-19 patients with high inflammatory burden and therefore preventing multi-organ dysfunction. Interestingly, vitamin D has also been shown to up-regulate the expression of IL-10 which is thought to be a potential treatment target for COVID-19 (43-46). These potential immunologic effects of vitamin D is supported by multiple studies that reported the impact of vitamin D supplementation on reduction of inflammatory burden in T_H1 and/or T_H17 mediated autoinflammatory diseases such as rheumatoid arthritis (47), psoriasis (48, 49), multiple sclerosis (50) and inflammatory bowel disease (51). In addition, it has been suggested that activation of the VDR in the pulmonary stellate cells might play a role in suppressing inflammation and fibrotic changes in the lungs of COVID-19 patients (52).

Third, $1,25(OH)_2D$ has been shown to regulate the renin-angiotensin-aldosterone (RAAS) system (**Figure 3**) (53, 54), and the effects are thought to be different among tissues. In an animal model, oral administration of alfacalcidiol (1α-hydroxyvitamin D) was shown to inhibit ACE2 expression, which is the main receptor entry of SARS-CoV-2, in the renal tubular cells (54, 55). Therefore, $1,25(OH)_2D$ likely exerts the same biologic on the kidney and therefore may be protective against COVID-associated kidney injury by reducing viral entry into the cell. It has been shown that SARS-CoV-2 infection downregulate ACE2 in the lungs (56). This causes accumulation of angiotensin II, which is believed to play a role in the development of ARDS, myocarditis, and cardiac injury the major severe complications of COVID-19 (56). In the lipopolysaccharide-induced acute lung injury animal model, $1,25(OH)_2D$ was shown to suppress renin, ACE and angiotensin II expression and increase ACE2 expression (57, 58). These effects could potentially reduce the accumulation of angiotensin II and therefore reduce the risk of ARDS and cardiac injury especially in COVID-19 patients who have pre-existing dysregulation of the RAAS system such as those with underlying hypertension, heart failure and renal insufficiency (59). Additionally, a mechanistic model generated from gene expression data of cells in bronchoalveolar lavage fluid from COVID-19 patients and controls have suggested that the inhibitory effect of $1,25(OH)_2D$ on renin expression may result in decreased flux of angiotensin I to angiotensin-

(1-9) (60). This mechanism is thought to help mitigate bradykinin storm, which has been shown to underlie the multiple organ dysfunction in COVID-19 (60).

Another action of vitamin D is its pleiotropic effects against endothelial cell dysfunction and vascular thrombosis, which may mitigate vascular leakage secondary to systemic inflammatory response and prevent COVID-associated arterial and venous thrombosis (61-63). It has been shown in the primary dermal human microvascular endothelial cell model that vitamin D_3, $25(OH)D_3$ and $1,25(OH)_2D_3$ stabilized vascular endothelial membranes via a non-genomic pathway (61). Additionally, vitamin D_3, which normally circulates at about 100 times higher concentration than $1,25(OH)_2D_3$, was at least 10 times more potent than $1,25(OH)_2D_3$ and more than 1,000 times more potent than $25(OH)D_3$ in stabilizing the endothelium (61). Furthermore, it has been shown in a uremic rat model that paricalcitol [19-nor-$1,25(OH)_2D_2$] could prevent the development of endothelial intracellular gaps and reduce endothelial damage (62). Finally, vitamin D is known to exert direct and indirect antithrombotic activities by controlling the expression of multiple genes involved in the coagulation pathway (63).

Despite multiple mechanisms suggesting potential benefits of vitamin D for COVID-19, $1,25(OH)_2D$ is known to inhibit plasma cell differentiation and reduce immunoglobulin production by B-cells in the settings of autoimmune disorders (30, 64, 65). It is still unclear whether this biologic action could dampen the production of neutralizing antibodies and be detrimental in the setting of response to COVID-19 infection or COVID-19 vaccine. Further studies are required to investigate this aspect of vitamin D actions.

Pre-COVID evidence from clinical studies

The outbreak of influenza infection is seasonal and usually occurs in the winter in high-latitude areas but is sporadic throughout the year in tropical areas (66, 67). The most likely explanation of this phenomenon is the seasonal variation of temperature, humidity and intensity of ultraviolet radiation (68-70). Another possible explanation for this outbreak pattern is the seasonal variation in serum concentrations of 25(OH)D of the population that reach the lowest levels in the winter (71). This notion is supported by several studies that have shown the independent association between low concentration of serum 25(OH)D and incidence and severity of acute respiratory viral infection. For example, a cohort study in healthy adults demonstrated approximately 50% reduction in the risk of incident acute respiratory tract infection in those with serum 25(OH)D concentrations of ≥38 ng/mL (95

nmol/L) (72). A case-control study in 469 New Zealand children aged <2 years demonstrated that those requiring hospitalization for acute respiratory infection had a significantly 1.7-time higher odds of vitamin D deficiency than those with mild illnesses (73). To illustrate the causal association, a randomized controlled trial gave 1200 IUs of vitamin D_3 per day or placebo to 167 Japanese schoolchildren for 4 months and revealed that those who received vitamin D_3 supplementation had a significantly lower risk of influenza A infection compared with the placebo group (RR 0.58; 95% CI: 0.34 – 0.99) (74). A more recent meta-analysis of 25 randomized controlled trials showed that supplementation of vitamin D_2 or D_3 can protect against the development of acute respiratory tract infection compared with placebo (adjusted OR 0.88; 95%CI: 0.81 – 0.96) (75). The protective effects were more pronounced in those with baseline 25(OH)D concentrations of less than 10 ng/mL, or 25 nmol/L (adjusted OR 0.30; 95%CI: 0.17 – 0.53) (75). It should however be noted that there was moderate statistical heterogeneity in this main meta-analysis, with the I^2 value of 53.3%, and that most of the individual clinical trials included in the meta-analysis failed to demonstrate statistical significance of the impact of vitamin D supplementation (75).

Prior to the COVID-era, sepsis is one of the major causes of morbidity and mortality among hospitalized patients in the intensive care unit (76). A number of studies have shown the association between low concentrations of serum 25(OH)D increased unfavorable outcomes in sepsis and critically ill patients (77, 78). However, the association between vitamin D status and sepsis outcomes might be bi-directional as it is also probable that low serum 25(OH)D concentrations in patients with severe sepsis could be secondary to systemic inflammation that increases the activity of the 25(OH)D-24-hydroxylase that catabolizes 25(OH)D as well as causes extravascular leakage of the vitamin D-binding protein (79, 80). It should be noted that randomized clinical trials that investigated the impact of vitamin D supplementation on clinical outcomes of sepsis and critical illness have yielded mixed results. In a pilot study in 31 vitamin D-deficient patients who were on mechanical ventilations, administration of a single dose of enteral 500,000 or 250,000 IUs of vitamin D_3 was found to decrease hospital length of stay compared with placebo (81). In another randomized controlled trial that gave enteral 540,000 IUs of vitamin D_3 followed by monthly maintenance doses of 90,000 IU for 5 months or placebo to 475 vitamin D-deficient critically ill patients, a significant decrease in hospital mortality was observed in the subgroup of 200 patients with serum 25(OH)D<12 ng/mL, or 30 nmol/L (HR 0.56; 95%CI: 0.35 – 0.90) (82). On the other hand, in a larger clinical trial in 1,360 patients with critical illness, administration of a single

dose of enteral 540,000 IUs of vitamin D_3 was not superior to placebo in reducing the risk of mortality and other clinical outcomes (83). This negative result may suggest that it is too late for the critically ill patients to benefit from vitamin D supplementation and that vitamin D has to be given at the earlier stages of disease to demonstrate its survival benefit (84, 85).

Current evidence on vitamin D and COVID-19

Multiple observational studies have reported the link between vitamin D status or serum 25(OH)D concentrations and risk of acquiring COVID-19 in many countries worldwide. For example, a study using a national clinical laboratory database of the United States of 191,779 patients, SARS-CoV-2 positivity is strongly and inversely associated with circulating 25(OH)D concentrations, although the analysis was limited to one SARS-CoV-2 result per patient. The observed relationship was found to persist across latitudes, races, ethnicities, both sexes, and age ranges (86) (**Figure 4**). This result is in line with that of a retrospective cohort study showing that deficient vitamin D status was associated with an increased risk of positive test for COVID-19 [RR 1.77; 95% CI, 1.12 – 2.81] with likely sufficient vitamin D status after adjusting for potential confounders (87). Another study in 50 hospitalized COVID-19 Korean patients and 150 age- and sex- matched controls showed that the COVID-19 patients were about 3 times more likely to be severely vitamin D-deficient [25(OH)D <10 ng/mL or 25 nmol/L] than the control group (88). Another populational-based study in 782 Israeli COVID-19 patients and 7,025 controls showed that vitamin D deficiency was independently associated with approximately 1.5 times higher odds of COVID-19 test positivity [adjusted OR 1.50; 95%CI: 1.13 – 1.98] (89). In a study of 216 COVID-19 Spanish patients and 197 population-based controls, vitamin D deficiency [25(OH)D <20 ng/mL or 50 nmol/L] was found to be about 1.7 times more prevalent in COVID-19 cases than in the control group. Moreover, serum 25(OH)D concentrations were significantly lower in COVID-19 patients after adjusting for potential confounders (90). Nonetheless, a cohort study in 347 Italian hospitalized patients with positive and negative COVID-19 test showed no association between vitamin D status and COVID-19 test positivity (90). This negative finding is likely due to the fact that, unlike those of the other studies, hospitalized patients were recruited to be the control group (91). A study using data from the United Kingdom biobank consisting of 348,598 participants including 449 confirmed COVID-19 patients reported that vitamin D was associated with COVID-19 infection univariately, but not after adjustment for confounders. However, this study utilized serum concentrations of 25(OH)D measured during 2006 – 2000, which may not accurately reflect current vitamin D status (92).

In addition to the promising data on the relationship between vitamin D status with risk of acquiring COVID-19, a growing amount of evidence from multiple observational studies have reported the connection between vitamin D status and risks of severity in COVID-19 patients. A meta-analysis of 27 studies published in reported that vitamin D deficiency in COVID-19 patients was significantly associated with higher risks of severe infection [OR 1.64; 95%CI: 1.30 – 2.09], hospitalization [OR 1.81; 95%CI: 1.42 – 2.21] and mortality [OR 1.92; 95%CI: 1.06 – 2.58] (93). Several more recent studies in many different regions worldwide have addressed the same question with relatively inconsistent results (93-100). This could be due to different patient characteristics and study design across the studies.

There are some issues that are worth noting while processing the evidence. First, vitamin D deficiency is associated with presence and disease burden of several comorbidities such as cardio-metabolic disorders, chronic kidney disease and obesity (101-103). Therefore, the observed association might be in part confounded by these factors, although most studies have already attempted to address this with multivariate analysis (98-100, 104). Second, the association between vitamin D status at the time of hospitalization and outcomes of acute inflammatory illness is likely due in part to reverse causation. Low level of serum 25(OH)D could also be secondary to systemic inflammatory response which results in vascular leakage of vitamin D-binding protein and albumin as well as increased catabolism of 25(OH)D (105, 106). Third, vitamin D might benefit each individual differently as significant inter-individual difference in responsiveness to vitamin D supplement has been reported (33-35). Additionally, aged individuals may benefit from vitamin D more than young adults as they tend to have higher inflammatory burden of COVID-19. This notion is supported by the observation in some studies that showed a stronger association between vitamin D status and COVID-19 severity in elderly patients (93, 107). Finally, some studies that reported positive association utilized previous laboratory data (86, 89, 92) and use of diagnostic code of vitamin D deficiency from the medical record database to define vitamin D status (98). It is likely that an individual who was found to have vitamin D deficiency prior to the infection would have been treated for vitamin D deficiency and became vitamin D repleted by the time they were infected. This indicates that there might be the legacy effect of being vitamin D-sufficient and that raising serum 25(OH)D concentrations over a short period of time might not be as effective as maintaining serum 25(OH)D concentrations in a preferred range of 40-60 ng/mL (100 – 150 nmol/L) over the long term (12).

Given the promising evidence on the potential benefit of vitamin D against COVID-19, a number of ongoing randomized controlled trials have been conducted with the aim to investigate the impact of vitamin D supplementation of different forms and dosing regimens. A pilot randomized clinical trial that gave oral 25(OH)D_3 (calcifediol) or placebo to 76 COVID-19 patients and showed that the treatment group had a markedly reduced rate of intensive care unit admission (2% vs. 50%, $p<0.001$) (108). However, in a larger randomized controlled trial giving 240 hospitalized patients with moderate to severe COVID-19 200,000 IUs of vitamin D_3 or placebo, there were no differences in length of hospital stay, in-hospital mortality, admission to intensive care unit or mechanical ventilation requirement (109). This emphasizes that the immunomodulatory effects of vitamin D are likely to be the results of its long-term rather than short-term actions.

Recommended serum 25-hydroxyvitamin D concentrations to help fight the COVID 19 pandemic

It is largely controversial as to what concentration of serum 25(OH)D would provide optimal benefit for bone health, overall health benefits and prevention against COVID-19. Serum 25(OH)D concentration of higher than 15 – 20 ng/mL (37.5 – 50 nmol/L) would be sufficient for prevention of rickets, osteomalacia and symptomatic hypocalcemia (110). Notably, hypocalcemia is shown to be highly prevalent and associated with hospitalization in COVID-19 patients. Whether and how much sufficient level of serum 25(OH)D would be protective against hypocalcemia in COVID-19 patients requires further investigations (111). However, it is recommended that serum 25(OH)D concentration should be above 30 ng/mL (75 nmol/L) to maximize the calcemic effects of vitamin D and minimize the risk of secondary hyperparathyroidism that predisposes to osteoporosis (12). It is worth considering the historical evidence to postulate vitamin D status in our hunter gatherer forefathers. Hadza tribesmen and Maasai herders were reported to have serum concentrations of 25(OH)D in the range of 40 – 60 ng/mL (100 – 150 nmol/L) (112-114). This range is in line with that reported not only in population-based studies to be associated with the lowest risk of chronic diseases and all-cause mortality (11, 114-117), but also in recent studies to be associated with decreased risks of COVID-19 infection and its severity (86-90, 93). With minimal sunlight exposure, an adult would require ingestion of 4,000 – 6,000 IUs of vitamin D_3 or vitamin D_2 daily to maintain serum 25(OH)D in the preferred range of 40 – 60 ng/mL (100 – 150 nmol/L) (12). Obese adults require 2-3 times more vitamin D to maintain the same serum concentrations of 25(OH)D (12, 118).

On average, approximately 40% and 60% of children and adults have circulating concentrations of 25(OH)D <20 ng/mL (50 nmol/L) and <30 ng/mL (75 nmol/L), respectively (119). This already high prevalence of vitamin D deficiency/insufficiency tends to be further aggravated by the lack of sunlight exposure and outdoor activity as a result of the pandemic lockdown. Thus, patients hospitalized with COVID-19 are likely to be vitamin D-deficient or insufficient, and, therefore, it is reasonable to institute as standard of care to measure serum 25(OH)D level and to give at least one single dose of 80,000 – 100,000 IUs of vitamin D to all vitamin D-deficient [25(OH)D <20 ng/mL or 50 nmol/L] or insufficient [25(OH)D 20- <30 ng/mL or 50 -<75 nmol/L] COVID-19 patients with a normal body mass index and at least 200,000 IUs for those with obesity (body mass index >30 kg/m^2) after being hospitalized (12, 85, 108). It is noteworthy that optimal magnesium status may be important for optimizing vitamin D status (120, 121). Therefore, maintaining magnesium status by giving magnesium supplementation with high-dose vitamin D may benefit in this situation. Additionally, corticosteroids have become a mainstay treatment for COVID-19 in patients with high inflammatory burden. It should be noted that corticosteroids and some other medications (e.g., antiepileptics and antiretrovirals) affects the steroid and xenobiotic receptor or the pregnane X receptor, causing increased catabolism of 25(OH)D and $1,25(OH)_2D$ into inactive water-soluble carboxylic acid derivatives (12). Thus, patients who receive any of these medications should also be given an increased dose of vitamin D of 200,000 IUs (12). Finally, if hospitalized more than 1 week, with minimal sunlight exposure and dietary intake of vitamin D, they should continue to receive the daily or the equivalent weekly dose of about 2000 – 5000 IUs per day and 6000 – 10,000 IUs per day for those with obesity or receiving corticosteroids (12). This strategy is proposed to ensure serum 25(OH)D level of at least 30 ng/mL (75 nmol/L) throughout hospitalization. Further clinical trials are required to examine the clinical benefits or risks of this strategy specifically on COVID-19-related outcomes.

Conclusion

Vitamin D is known not only for its importance for calcium and phosphate metabolism but also for its biologic actions on immune modulation. This is because of the presence of the vitamin D receptor in most types of cells, especially the immune cells including activated T and B lymphocytes and macrophages. Experimental studies have shown that vitamin D exerts several biological activities that are thought to be protective against COVID-19. These include the immunomodulatory effects on the innate and adaptive immune

systems, the regulatory effects on renin-angiotensin-aldosterone-system in the kidneys and the lungs, and the protective effects against endothelial dysfunction and thrombosis. Prior to the COVID-era, it has been reported that vitamin D supplementation is beneficial in protecting against risk of respiratory viral infection and may improve outcomes in sepsis and critically ill patients. There are a growing number of data suggesting the link between serum 25(OH)D concentrations and COVID-19 infectivity and severity. Although it is still pending for the results from randomized clinical trials aiming to prove the benefit of vitamin D supplementation for these purposes, there is no downside to increasing vitamin D intake and having sensible sunlight exposure to maintain serum 25(OH)D at least 30 ng/mL (75 nmol/L) and preferably at 40 – 60 ng/mL (100 – 150 nmol/L) (12) to achieve optimal health benefits of vitamin D and minimize the risk of COVID-19 infection and its severity.

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Figure legends

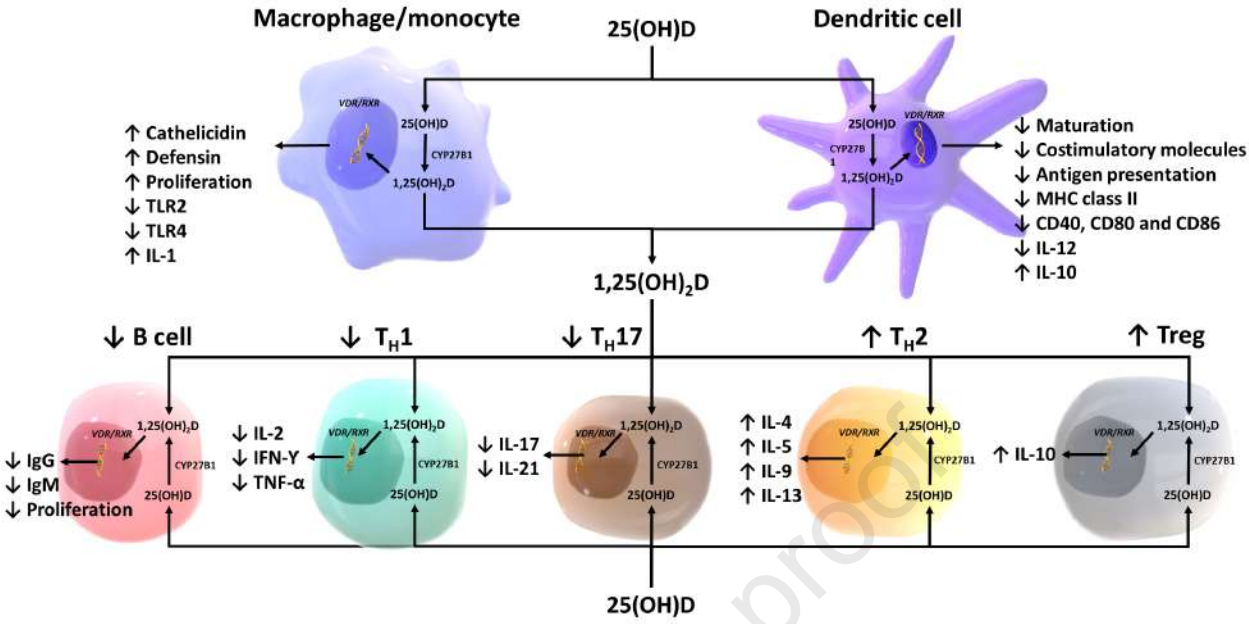
Figure 1. Schematic representation of paracrine and intracrine function of vitamin D and its metabolites and actions of 1,25-dihydroxyvitamin D on the innate and adaptive immune systems. Abbreviation: 1,25(OH)2D: 1,25-dihydroxyvitamin D; 25(OH)D: 25-hydroxyvitamin D, IFN-Y: interferon- Y; IL: interleukin; MHC: membrane histocompatibility complex, TH1: T helper 1; TH2: T helper 2; TH17: T helper 17; Treg: regulatory T cell, TNF-α: Tumor necrosis factor- α; TLR2: toll-like receptor 2; TLR4: toll-like receptor 4. Reproduced with permission from Holick MF, 2020.

Figure 2. Heatmaps of vitamin D responsive genes whose expression response variation in 6 vitamin D-deficient subjects taking 10,000 international units per day of vitamin D3 for 6 months showing that 3 subjects had a robust response in gene expression compared to the other 3 subjects who had minimum to modest responses even though these subjects raised their blood levels of 25(OH)D in the same range of ~60 – 90 ng/mL. Abbreviation: 0m: 0 month; 6m: 6 months; 25(OH)D: 25-hydroxyvitamin D; PTH: Parathyroid hormone. Reproduced with permission from Holick MF, 2019.

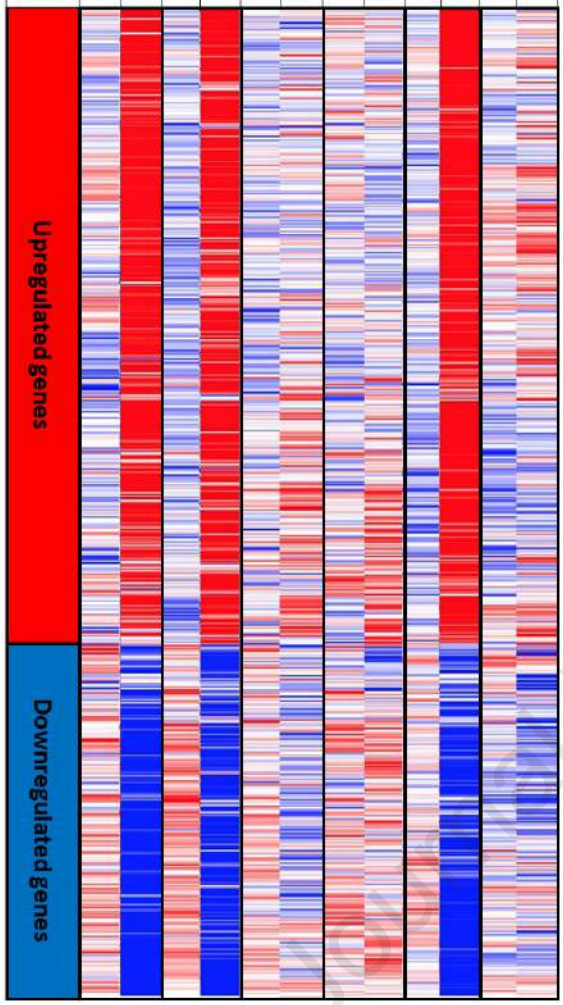
Figure 3. Schematic representation of the effects of $1,25(OH)_2D$ on the renin-angiotensin-aldosterone system. SARS-CoV-2 uses the ACE2 as the main receptor entry site and downregulates ACE2 in the lungs. This causes the accumulation of angiotensin II which causes inflammation and apoptosis in the lungs, and systemic vasoconstriction by interacting with the AT_1 receptor, leading to COVID-related complications including ARDS, myocarditis and cardiac injury. $1,25(OH)_2D$ inhibits renin and ACE, and induces the expression of ACE2 in the lungs, thereby reducing the accumulation of angiotensin II. Inhibition of renin expression may also result in decreased flux of angiotensin I to angiotensin-(1-9), thereby mitigating bradykinin storm Additionally, $1,25(OH)_2D$ may inhibit

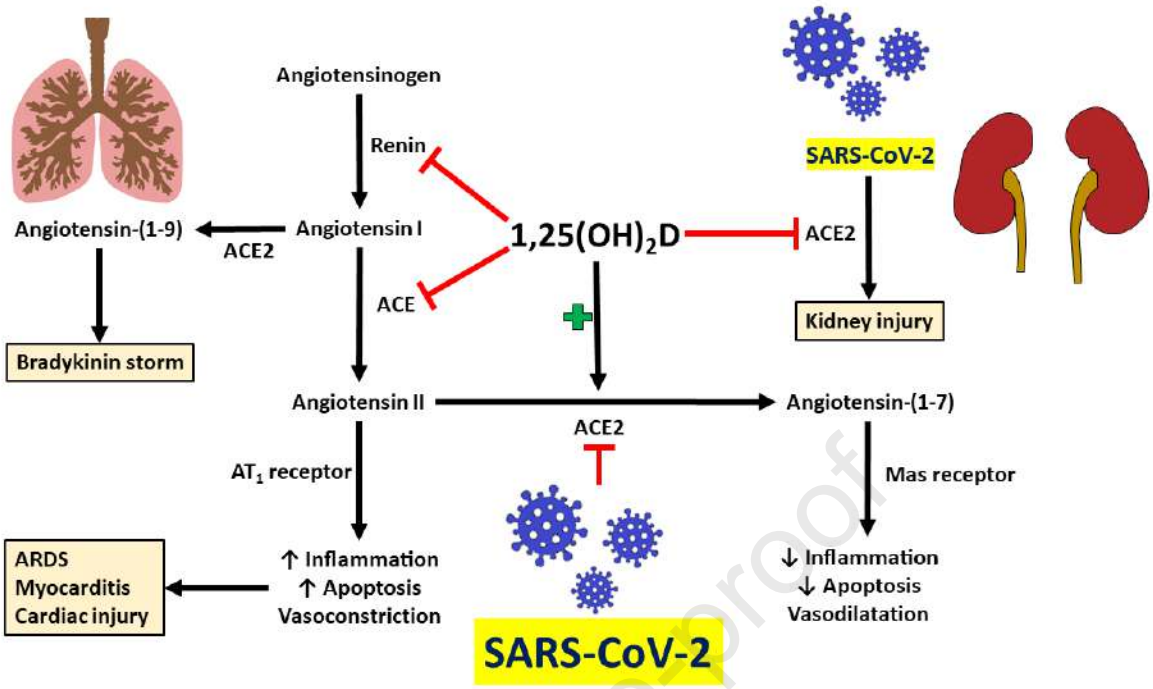
ACE2 expression in the renal tubular cells, which is thought to be protective against COVID-associated kidney injury by reducing the viral direct cytopathic effects on the cell. Abbreviations: 1,25-dihydroxyvitamin D; $1,25(OH)_2D$; Angiotensin converting enzyme: ACE; Angiotensin converting enzyme 2: ACE2; AT_1 receptor: Angiotensin II type 1 receptor; SARS-CoV-2: Severe acute respiratory distress syndrome coronavirus 2 (Copyright Holick, 2021).

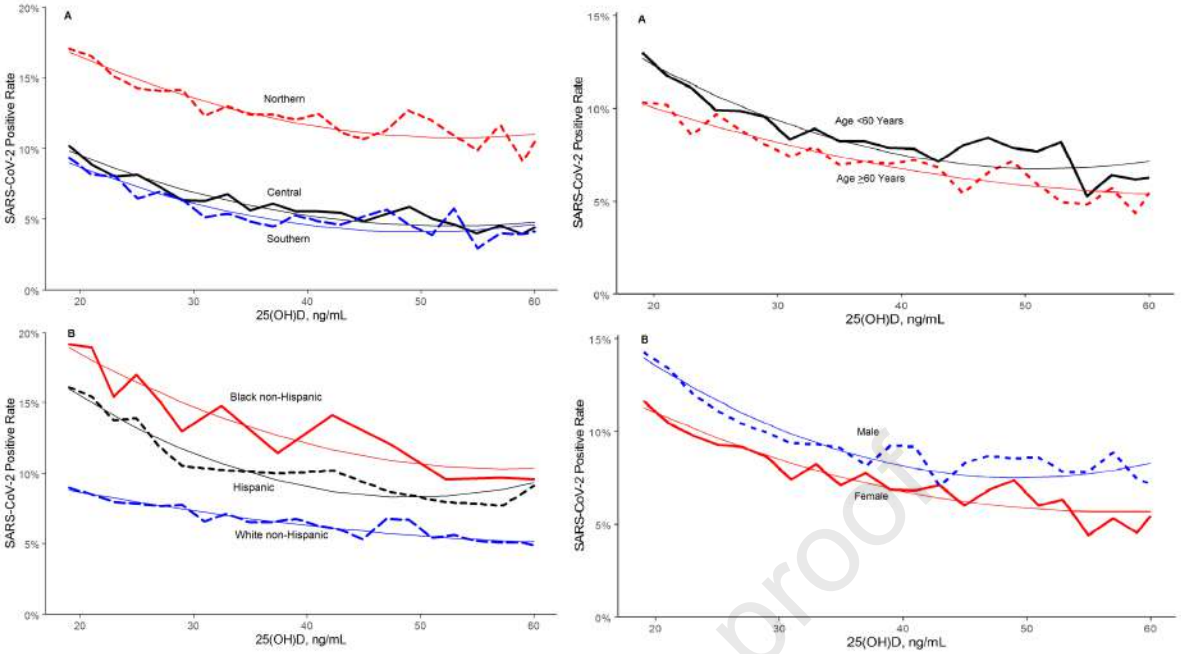
Figure 4. SARS-CoV-2 nucleic acid amplification test positivity rates and circulating 25-hydroxyvitamin D levels by (A) latitude region, (B) Predominately Black non-Hispanic, Hispanic, and White non-Hispanic zip codes, (C) age group and (D) sex. Smooth lines represent the weighted second order polynomial regression fit to the data associating circulating 25(OH)D levels (x-axis) and SARS-CoV-2 positivity rates (y-axis). Copyright Kaufman 2020 with permission.



ID	34		46		56		66		68		73	
Time	0m	6m	0m	6m	0m	6m	0m	6m	0m	6m	0m	6m
25(OH)D	20	56	14	70	21	87	18	88	23	96	14	84
PTH	39	13	46	27	34	24	59	12	32	43	20	15







Highlights

- Vitamin D is an immunomodulatory agent that is thought to be protective against severity of COVID-19.
- There are a growing number of data connecting COVID-19 infectivity and severity with vitamin D status.
- It is advisable to maintain serum 25-hydroxyvitamin D in the range of 40 – 60 ng/mL to minimize the risk of COVID-19 infection and its severity.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Michael F. Holick is a consultant for Quest Diagnostics Inc., Biogena Inc. and Ontometrics Inc, and on the speaker's Bureau for Abbott Inc.